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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,952	03/22/2002	Stephen H. Leppla	15280-4051US	4741

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No.	Applicant(s)	
	10/088,952	LEPPLA ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7-9,11-14,18-22 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,8-9,11-14,18-22 and 25-30* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/26/2006 has been entered.

Claims 1, 4, 7-9, 11-14, 18-22 and 25-30 are currently pending and under consideration.

The Declaration under 37 CFR 1.132 filed on 2/28/2006 by Dr. Leppla is insufficient to overcome the rejection of claims 1, 4-5, 8, 11-14, 18-22 and 25-29 based upon 35 U.S.C. 103(a) as being unpatentable over Leppla et al. (IDS, 1997) in view of Bayley *et al.* (IDS, 1998) as set forth in the last Office action for the reasons set forth below.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 8-9, 11-14, 18-22 and 25-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are inclusive of a genus of mutated protective antigen proteins comprising a plasminogen activator-recognized cleavage site in place of the native protective antigen furin recognized cleavage site. Therefore, the claims encompass a genus of molecules defined solely by its principal biological property, e.g., having a plasminogen activator-recognized cleavage site, which is simply a wish to know the identity of any material with that biological property. However, the written description in this case only sets forth mutated protective antigen proteins comprising a

plasminogen activator-recognized cleavage site in place of the native protective antigen furin recognized cleavage site, wherein the uPA recognized cleavage site is selected from the group consisting of the amino acid sequence of SEQ ID NO: 4, 5 and 6.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164).

The specification teaches (page 7, lines 1-3) that specific plasminogen activator-recognized cleavage sites of the invention include, but are not limited to, PCPGRWGG (SEQ ID NO:4), PGSGRSA (SEQ ID NO:5), PGSGKSA (SEQ ID NO:6), and PQRGRSA (SEQ ID NO:7). Specifically, the specification teaches (page 21, lines 6-10) that the plasminogen activator uPA recognizes the amino acid sequence of SEQ ID NO: 5 and 6, tPA recognizes the amino acid sequence of SEQ ID NO: 7 and both uPA and tPA recognize the amino acid sequence of SEQ ID NO: 4. Thus, while the specification reasonably conveys a protective antigen having the uPA recognized cleavage site selected from the group consisting of SEQ ID NO: 4, 5 and 6 in place of the native furin cleavage site, as noted above, the claims encompass a genus of molecules defined solely by its principal biological property, e.g., having a plasminogen activator-recognized cleavage site, which is simply a wish to know the identity of any material with that biological property. Accordingly, there is insufficient written description encompassing a "plasminogen activator-recognized cleavage site" because the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics of a "plasminogen activator-recognized cleavage site" are not set forth in the specification as-filed. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by

means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of plasminogen activator-recognized cleavage sites that encompass the genus nor does it provide a description of structural features that are common to the genus. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus of plasminogen activator-recognized cleavage sited, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it

is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a mutated protective antigen proteins comprising a plasminogen activator-recognized cleavage site in place of the native protective antigen furin recognized cleavage site, wherein the uPA recognized cleavage site is selected from the group consisting of the amino acid sequence of SEQ ID NO: 4, 5 and 6, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 8-9, 11-14, 18-22 and 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leppla et al. (IDS, 1997) as evidenced by Klimpel et al. (PNAS 1992; 89: 10277-10281) in view of Bayley *et al.* (IDS, 1998).

Leppla *et al.* teach (column 115, lines 410-63) a method for targeting compounds having a desired biological activity not present on native anthrax lethal factor (LF) to a specific cell population, comprising: a) administering to the cell population a first compound comprising a first protein consisting essentially of: i) the translocation domain and the anthrax lethal factor (LF) binding domain of the native anthrax protective antigen (PA) protein, and ii) a ligand domain that specifically binds the first protein to a target on the surface of the cell population to bind the first compound to said surface; and b) administering to the resultant cell population a second compound

comprising a fusion protein or conjugate consisting essentially of: i) the anthrax protective antigen (PA) binding domain of the native anthrax lethal factor (LF) protein, chemically attached to ii) a biological activity-inducing polypeptide to bind the second compound to the first compound on the surface of the cell population, internalize the second compound into the cell population, and effect the activity of the polypeptide therein. The patent further teaches (Column 116, lines 42-44, 53-56, and 63-64) that the ligand domain of the first compound can be either the ligand domain of the native anthrax protective antigen (PA) protein or growth factor, or an antibody, wherein the antibody is a single chain antibody. Furthermore, Leppla *et al.* disclose (column 115, lines 64-67 and column 116, lines 40-41) that the anthrax protective antigen (PA) binding domain of the second compound comprising at least the first 254 amino acid residues but less than all of the amino acid residues of the native anthrax lethal factor. Moreover, the patent teaches (column 116, lines 51-52) that the second compound may comprise the anthrax protective antigen (PA) binding domain of the native anthrax lethal factor (LF) protein chemically attached to a polypeptide through a peptide bond. In addition, Leppla *et al.* teach (column 116, lines 49-52 and 57-62) that the polypeptide of the second compound is an enzyme or a toxin, wherein the toxin can be Pseudomonas exotoxin A (PE), A chain of Diptheria toxin, or shiga toxin. With regards to Pseudomonas exotoxin A, the patent teaches (column 17, lines 15+) that anthrax lethal toxin is linked to the ADP-Ribosylation Domain of Pseudomonas exotoxin. Leppla *et al.* also disclose (Abstract, last sentence) proteins including an anthrax protective antigen which has been mutated to replace the trypsin cleavage site with residues recognized specifically by the HIV-1 protease. Specifically, the patent teaches (column, 11, lines 10-13) PA proteins which have been mutated to replace R164 to 167 with an amino acid sequence recognized by the HIV-1 protease. In addition, the patent teaches (column 1, lines 24-26) that in a therapeutic or diagnostic setting, the used of an sFv may offer attractive advantages over the use of monoclonal antibodies. Lastly, Leppla *et al.* teach (column 15, lines 27-37) that this methodology can be used to specifically killing a tumor cell in a subject. Thus while Leppla et al. do not specifically teach that amino acid residues R164-167 is the furin recognized cleavage site of native protective antigen, the claimed limitation does not appear to result in a manipulative difference when compared to the prior art because as evidenced by Klimpel et al. residues 164 to 167 of PA is a furin recognized cleavage site (abstract).

Leppla *et al.* does not disclose a mutated protective antigen comprising a plasminogen activator-recognized cleavage site in place of the native protective antigen furin-recognized cleavage site. Nor do Leppla et al. teach that the cancer is a melanoma.

Bayley *et al.* teach (column 12, lines 13+) the construction of Ab-αHL conjugates and mutated two chain αHL conjugates, wherein a protease can be employed as an activator of inactive compounds, e.g. plasminogen activator, specifically urokinase-type plasminogen activator (uPA). Specifically, the patent teaches (column 12, lines 13+) that because cancer cells have been shown to secrete plasminogen activator, the protease cleavage site for plasminogen activator can be incorporated into the conjugate for specific activation of this cell type. In addition, the patent teaches that uPA is highly expressed in melanoma cells (column 13, lines 1-5).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to incorporate a plasminogen activator-protease cleavage site in place of the native protective antigen furin-recognized cleavage site as a way of targeting a compound to a cancer cell over-expressing a plasminogen activator or plasminogen activator receptor. One would have been motivated to make this substitution because Bayley *et al.* teach that it is well known in the art that a plasminogen activator, such as uPA, can be employed as an activator of an inactive agent such as the protective antigen protein of Leppla *et al.*. One of ordinary skill in the art would have reasonable expectation of success that by combining the plasminogen activator-recognized cleavage site of Bayley *et al.* with the method of specifically targeting a bioactive compound taught by Leppla *et al.*, one would achieve a method of specifically targeting a compound to a cancer cell because as evidenced by Bayley et al., cancer cells have been shown to secrete plasminogen activator.

In response to this rejection, Applicants assert that the cited references alone or in combination do not render the presently claimed invention obvious. As set forth in the Declaration of Dr. Leppla, Applicants assert that one of skill in the art would not have a reasonable expectation of success to practice the claimed invention based on the cited references. For example, Applicants assert that, as described by Dr. Leppla, *Leppla et al.* discloses that a compound can be delivered to a cell using a binary bacterial toxin (i.e., native anthrax protective antigen or an anthrax protective antigen with an HIV-1 protease cleavage site in place of the native protective antiegen cleavage site), but does not disclose or suggest a mutant protective antigen comprising a plasminogen activator-recognized cleavage site in place of the native protective antigen furin-recognized cleavage site.

However, Applicants assert that Bayley et al. does not remedy the deficiency in Leppla et al. because Bayley et al. merely disclose that a uPA cleavage site can be incorporated into a polypeptide that does not contain such a cleavage site. Moreover, Applicants assert that, as explained by Dr. Leppla, even if one of skill in the art were to combine the disclosures of Leppla et al. and Bayley et al. there would be no reasonable expectation of success in being able to practice the presently claimed methods because binding of a protease to its cleavage site and subsequent proteolytic cleavage is dependent on the three dimensional structure of the proteins. As such, Applicants assert that the Declaration sets forth that one of skill in the art would not have expected that the uPA overexpressed on the surface of a target cell and the uPA cleavage site on the mutant protective antigen would have come into contact with each other. For example, Applicants submit that, as explained in the Declaration, the uPA cleavage site in the mutant PA might not be positioned at an appropriate distance from the cell membrane to contact the uPA on the surface of the target cell. Lastly, Applicants submit that the experimental evidence presented in Dr. Leppla's declaration demonstrates that the claimed methods are surprisingly effective. For example, Applicants assert that the mutated protective antigens of the presently claimed invention are particularly effective for delivering a compound to target cells which overexpress uPA. As such, Applicants assert that the experiments unequivocally demonstrate that the mutant protective antigens of the invention can be used for in vivo delivery of a compound to a target cell overexpressing uPA.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants assertion that Bayley et al. do not remedy the deficiencies in Leppla et al., the examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the ad (National Steel Car v. Canadlan Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the ad, rather than by their specific disclosures. In re Bozek, 163

USPQ 545 (CCPA 1969). In the instant case, Leppla et al. disclose a method for targeting compounds having a desired biological activity not present on native anthrax lethal factor (LF) to a specific cell population, comprising: administering a protective antigen which has been mutated to replace the trypsin cleavage site, e.g., furin cleavage site, with residues recognized specifically by the HIV-1 protease, wherein this methodology can be applied to specifically killing a tumor cell in a subject, whereas Bayley et al. teach that because cancer cells have been shown to secrete plasminogen activator, the protease cleavage site for plasminogen activator can be incorporated into a conjugate for specific activation by this cell type. As such, Bayley et al. provides the motivation to incorporate a plasminogen activator-recognized cleavage site into the mutated protective antigen taught by Leppla et al. Regarding Applicants assertion, as well as the Declarations assertion, that one of skill in the art would not have a reasonable expectation of success to practice the claimed invention, the Examiner acknowledges that the level of success if often difficult to predict in view of the three dimensional protein structure. However, the Examiner recognizes that emphasis is on a reasonable expectation of success in view of the references cited. In the instant case, Leppla et al. disclose targeting compounds having a desired biological activity not present on native anthrax lethal factor (LF) to a specific cell population, comprising: administering a protective antigen which has been mutated to replace the trypsin cleavage site, e.g., furin cleavage site, with residues recognized specifically by the HIV-1 protease, wherein this methodology can be applied to specifically killing a tumor cell in a subject, whereas Bayley et al. teach the incorporation of a uPA recognized cleavage site into an inactive compound is made active by a plasminogen activator expressed on the cell surface of tumor cells. As such, it is the Examiner opinion that one of ordinary skill in the art would have a reasonable expectation of success that that by combining the plasminogen activator-recognized cleavage site of Bayley *et al.* with the method of specifically targeting a bioactive compound taught by Leppla *et al.*, one would achieve a method of specifically targeting a compound to a cancer cell. Lastly, with regards to Applicants submission that the experimental evidence presented in Dr. Leppla's declaration demonstrates that the claimed methods are surprising effective and shows in vivo delivery of a compound to a target cell overexpressing uPA, the Examiner acknowledges and appreciates Applicants submission of these results. However, the Examiner recognizes that because experiments amount to a general allegation that the claims define a

patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references these arguments are considered to be moot.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Conclusion

Claim 7 is objected to as being dependent from rejected independent claim 1. In the instant case, the prior art does not appear to suggest that the plasminogen activator recognized cleavage site is SEQ ID NO: 5.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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BF

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